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14. ABSTRACT This project is focused on conducting the first randomized-controlled trial of Cognitive Enhancement Therapy (CET) in 54 verbal adults with autism spectrum disorders, and assessing the efficacy of this approach in comparison to an active Enriched Supportive Therapy (EST) intervention. Major findings to date include: 1) considerable and broad cognitive impairments prior to treatment in the ASD adults enrolled in this trial ($n = 54$), 2) significant improvements associated with CET in ameliorating these cognitive impairments and improving adaptive function, including employment, and 3) evidence of the neuroplastic effects of CET on brain function in support of cognitive enhancement in adult autism. Analyses of treatment effects to date suggest a significant advantage of CET for improving neurocognition ($d = .79$), social cognition ($d = .59$), major role function ($d = 1.02$), and employment ($d = .81$) compared to the EST control condition. In addition, analyses of changes in brain function have indicated significant increases in brain activity supporting social cognition and processing speed in participants treated with CET compared EST. These findings suggest both the need and potential for CET to be a significant treatment advance for verbal adults with autism. Importantly, improvements were found in daily life function and in brain circuitry supporting core abilities.					
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1. INTRODUCTION

This project constitutes the first clinical trial of a novel cognitive rehabilitation program, Cognitive Enhancement Therapy (CET), previously shown to be effective in improving adaptive function and work skills in patients with schizophrenia (Hogarty et al., 2004; Eack et al., 2009; Eack, Hogarty, Greenwald, Hogarty, & Keshavan, 2011), in a group of adults with autism spectrum disorders (ASD). Currently, there are few interventions for adults with ASD (Fitzpatrick, Minshew, & Eack, 2013), and none that are effective at remediating the broad range of information processing impairments characteristic of ASD. This project will randomize a total of 54 adults with ASD to CET ($n = 27$) or an Enriched Supportive Therapy (EST) control group ($n = 27$) and treat them for 18 months to examine the relative efficacy of CET compared to EST for remediating the core social and non-social information processing deficits that limit adaptive function and quality of life in adults with ASD. Specific aims of this project are to: (1) estimate the effects of CET and EST on cognition and behavior; (2) examine the durability of CET and EST effects on cognition and behavior 1 year after treatment completion; and (3) explore the effects of CET and EST on brain structure, function, and connectivity.

2. BODY

2.1. Overview of Study Infrastructure Development

This DoD-funded clinical trial is the first rigorous controlled study of CET and includes a comparison to an active EST intervention in adults with autism. The considerable progress that we have made already in this study is due to (1) the infrastructure support provided by the University of Pittsburgh Autism Center of Excellence (ACE) which was funded by the NICHD until 7/31/12; (2) the completed uncontrolled pilot trial of CET in 14 adults with ASD supported by the NIMH and the Commonwealth of Pennsylvania; and (3) early support provided by Autism Speaks to begin components of this trial while our application was being considered for funding by the DoD. Initial recruitment, diagnostic, and clinical trial infrastructure development was completely supported by the ACE. In August, 2010 Autism Speaks awarded us with a small grant to begin the development of a randomized-controlled trial of CET in verbal adults with autism based on promising preliminary findings from our uncontrolled trial of 14 adults that was funded by the NIMH. This early support provided by Autism Speaks allowed us to spend the first 6 months of the project developing the clinical infrastructure needed to conduct a randomized trial, including hiring and training our first full-time therapist, although no support for neuroimaging was provided. Importantly, after finalizing the development of this infrastructure we were able to enroll and randomize our first 12 of the many participants that the ACE had placed on a waiting list for this trial, which enabled this DoD-funded project to meet and exceed its aggressive recruitment and randomization schedule on a limited budget.

2.2. Task Progress and Accomplishments

This project was awarded and began on September 30, 2011. We have completed 36.0 months of the project and have made substantial progress toward accomplishing our aims. Most notably, we have completed recruitment and randomized 54 adults with ASD assigned to either CET ($n = 29$) or EST ($n = 25$), finished pre-treatment data collection with all randomized individuals, have begun treatment with these individuals, and are in the process of collecting post-treatment data on these participants to assess the efficacy of CET compared to EST in adults with autism. Given this progress, *we are on schedule in the conduct of this clinical trial.*

There have been no substantive modifications to the specific aims of this project during this year. However, we proposed an addition to Specific Aim #2 in our previous report. We will conduct 1-year post-treatment durability assessments on participants instead of 6-month post-treatment assessments to enhance the assessment of the long-term maintenance of treatment gains. Although these 1-year follow-up data will require a no-cost extension of this project to complete, a longer follow-up will provide a more rigorous test of treatment durability and are expected to establish compelling evidence for the long-term efficacy of CET and EST. In addition, due to support obtained for neuroimaging from the NIMH, and approval from DoD to expand the scope of this project, we have been able to include a sample of healthy control individuals for the imaging component of this study. Many of the fMRI tasks employed in this research are novel. Including these healthy control individuals will give us a normative sample for defining typical brain activity on these tasks to which the imaging data from the ASD participants in this trial can be compared. These normative data are essential for understanding the treatment effects of CET and EST on neural circuitry.

Progress and specific accomplishments with regard to the Statement of Work originally outlined in our proposal is summarized below:

Task 1 - Secure final IRB approvals at University of Pittsburgh, Carnegie Mellon University, and USAMRMC (mos 1-6). Institutional review board approvals have been secured for this clinical trial at the

University of Pittsburgh, Carnegie Mellon University, and the US Army Medical Research and Materiel Command. Ongoing revisions to the study protocol have been minimal. This year's Continuing Renewal Report to these human subjects organizations was submitted for review, and approval to renew the project for another year has been received from the University of Pittsburgh and Carnegie Mellon University IRBs; these approvals have been forwarded to the US Army Medical Research and Materiel Command along with renewal materials for approval. Strict surveillance over confidential data and human subjects research regulations outlined by the federal government, Belmont Report, and the Department of Defense has been maintained through weekly meetings to ensure data confidentiality and integrity.

Task 2 - Establish university accounts, subcontracts, and consultant contracts (mos 1-3). All university accounts have been established, including accounts at Western Psychiatric Institute and Clinic and the School of Social Work at the University of Pittsburgh, as well as with the Scientific Imaging and Brain Research Center at Carnegie Mellon University. Transactions on these accounts are regularly reviewed by the PI to ensure appropriate use of funds that are directly budgeted for this project.

Task 3 - Install subject tracking system (mos 1-3). A system for tracking participant recruitment and flow throughout this trial has been installed in a centralized SQL database that includes information on the number of times the participant was contacted for study participation, eligibility status, any exclusion criteria met, dates of screening, informed consent, and start of treatment, post-treatment due dates, treatment end dates, and notes regarding contact with participants and their status in the study.

Task 4 - Install data management tables compatible with NDAR; install GUID and randomization program (mos 1-3). NDAR-compatible data tables have been installed so that the data from this study can be transferred to NDAR when appropriate. The GUID system of assigning unique subject identifiers (IDs) has been installed for anonymous subject and data tracking. Randomization tables have been generated for the study, and are maintained, kept confidential, and subjects are assigned by the independent data management team to avoid bias in subject randomization.

Task 5 - Establish CET For ASD Clinical Trial procedures book; establish schedule of QC procedures (mos 1-3). A study procedures book has been created with all assessment forms, order of administration, role of study staff, and quality assurance procedures.

Task 6 - Train project coordinator (mos 1-6). A study coordinator (Summer McKnight - Research Specialist) for this project has been recruited, hired, and trained by the PIs and study staff. She has completed study protocol training by the PIs and is supervised weekly in the implementation and maintenance of these procedures. She has also received project coordinator training at Western Psychiatric Institute and Clinic and participant reimbursement training at the University of Pittsburgh Medical Center. The study coordinator has also been trained in the reliable collection of all neuropsychological and interview assessment data associated with this clinical trial by Drs. Minshew, Eack, and Greenwald and Mrs. Hogarty. Her training has been supplemented with specific neuropsychological training on the MATRICS Consensus Cognitive Battery at the Department of Psychology at Harvard University. She continues to be supervised in neuropsychological testing and clinical interviewing by Dr. Greenwald and Mrs. Hogarty.

Task 7 - Finalize fMRI tasks at CCBI Laboratory, Carnegie Mellon University (mos 1-6). All fMRI tasks have been created for the project in collaboration with Dr. Keller at the Center for Cognitive and Brain Imaging (CCBI) Laboratory, Carnegie Mellon University. This included the adaptation of Emotion Regulation, Perspective-Taking, and Inference Making tasks for this scanning facility, and the creation of a Processing Speed task to assess the effects of CET on neural functions associated with cognitive efficiency and speed of processing in ASD. All paradigms were programmed and refined to remove software bugs, and instruction scripts were created to ensure standardized delivery.

Task 8 - Pilot fMRI paradigms at SIBR, Carnegie Mellon University (mos 6-9). The four fMRI tasks developed and adapted for this project were piloted successfully using healthy volunteers at the Scientific Imaging and Brain Research Center (SIBR), Carnegie Mellon University. The perspective-taking fMRI task was adapted from a visual perspective-taking paradigm used in developmental psychology and previously pilot tested in patients with schizophrenia (Epley, Morewedge, & Keysar, 2004). Participants are asked to identify objects inside of a two-way grid array from the perspective of a virtual actor on the other side of the array. Purposely ambiguous trials are included that require the participant to shift from their perspective to that of the virtual actor in order to identify the correct item. This task has now been piloted and successfully implemented with adults with ASD with no major modifications. Recent results from studies using this task in schizophrenia have shown hypofunction in orbitofrontal and anterior cingulate cortical regions, as well as disconnectivity between fronto-temporal regions when engaging in perspective-taking during the task (Eack et al., 2013).

The emotion regulation fMRI task used in this study makes use of a negative emotion induction paradigm in which participants play a computer game to earn a prize. The game has several blocks, the first

consisting of easy trials where the participant wins points toward the prize, then difficult trials where the participant loses points toward the prize, and finally easy trials again when they ultimately win enough points to obtain the prize. This task allows for the induction of negative emotion and its regulation (during difficult trials) in a manner that evokes modulation of the emotion regulation neural circuitry of the brain, while at the same time still being an acceptable task for individuals with ASD. This task was previously piloted with adults with ASD (Perlman & Pelphrey, 2010), and we adapted it to the hardware used at SIBR for this project.

The inference making fMRI task used in this study has been previously employed by Dr. Marcel Just in studies of ASD (Mason, Williams, Kana, Minshew, & Just, 2008) and is included in this trial based on his recommendation that it provides a strong test of neural systems supporting theory of mind ability. The task requires participants to read paragraphs of different social scenarios that involve making inferences about the people depicted in the scenarios; adults with ASD have previously shown hypoactivation in the temporo-parietal-junction theory of mind (ToM) network when completing this task, providing support for this circuitry as the neural basis of the ToM aspect of the social deficit in autism. While the stimuli for the task were already developed, the task needed to be programmed in a standardized stimulus presentation software suite, which was carried out by our team.

Finally, the processing speed task was newly created for this project to capture the neural basis for the strong effects of CET on processing speed observed in our pilot ASD data, as well as on speed of processing in CET trials of patients with schizophrenia. This processing speed task was designed to replicate those activities used during neurocognitive training in CET and consists of visual reaction time tasks in which participants must respond to a visual (center light) cue as quickly as possible with the press of a button. The fMRI task involves a mixed blocked/event-related design in which participants perform separate blocks involving performance of the task at variable or fixed interstimulus intervals that employ either simple or choice reaction time tasks. This task needed to be completely programmed and piloted by our group, and was fully tested in healthy volunteers prior to beginning this project.

Task 9 - Revise study brochure and advertisements (mos 1-6). New study brochures and advertisements were created specifically for this trial that outlined the procedures involved, the content of both of the interventions, expected time commitments for each treatment, supports provided by the study, and funding by the Department of Defense. In addition to these brochures for families and clinicians, a social stories electronic slide show was created specifically for individuals with ASD. Individuals affected by ASD rely more heavily on visual information processing; the ability to meet the study staff and know the exact procedures involved in the study through this visual display greatly increases their comfort with the program. Families and individuals with ASD have noted repeatedly the helpfulness of this approach, which has served well as a recruitment and enrollment tool.

Task 10 - Faculty/staff recruitment activities (mos 1-24). The PIs and study staff have worked diligently to engage in recruitment activities throughout Pittsburgh and surrounding areas. This has included giving presentations on autism at local universities, clinical centers providing services, support groups, and other organizations that serve adults with ASD and their families. The longstanding connection of Dr. Minshew and the University of Pittsburgh Autism Center of Excellence to the community has strongly facilitated the ability of the program to reach out to this community and engage them in the importance of participating in this research for advancing the treatment of adults with autism. We have completed recruitment and accomplished our recruitment goals for this project.

Task 11 - Train new CET therapist (mos 1-6). A new therapist, Shannon A. Sloan, M.Ed., has been hired to expand the number of participants we can simultaneously treat in this trial to ensure we meet study milestones on time. She has experience in the treatment of individuals with ASD, as well as individual and group therapy modalities. She has read literature on autism and schizophrenia, as well as CET and EST interventions. Ms. Sloan is currently actively treating CET and EST cases, as well as receiving supervision by Drs. Eack, Greenwald, and Mrs. Hogarty in the implementation of these interventions.

Task 12 - Begin baseline testing and diagnosis of participants on waiting list (N = 31) (mos 6-9). Diagnostic testing of all study volunteers who met preliminary eligibility requirements has been completed. This included ADOS and ADI-R testing of all of the 31 participants on the study waiting list at the time this proposal was submitted, as well as 37 additional participants that accumulated on the waiting list during the time the study was under consideration for funding and since the project has begun. Of these individuals 35 (51%) met criteria for autism and 26 (38%) met criteria for autism spectrum disorder on the ADOS; 7 (10%) did not meet criteria for either autism or autism spectrum disorder. A total of 55 individuals received an ADI-R assessment; individuals not receiving this assessment either presented with no available family (e.g., both primary caregivers were deceased) or did not have a family member or close relative/friend willing to complete the assessment. Of the 55 individuals assessed with the ADI-R, 45 (82%) met criteria for autism and 10 (18%)

were below the threshold for full autism criteria. All diagnostic assessments were conducted at no cost to the study by ACE staff, reviewed by a trained psychologist, and diagnostic decisions were made based on all available evidence in consensus conferences with the study team.

Task 13 - Begin screening and diagnostic assessment of volunteers (N = 31) on CET wait list (mos 6-9). All 31 of the individuals who were on the study waiting list at the time of our application have been screened for eligibility and study enrollment. In addition, 189 subsequent referrals have also been screened (220 referrals total) to date. Bridge funding from Autism Speaks allowed us to begin screening this large number of potential participants while our application was under consideration for funding by the DoD. A total of 54 individuals meeting all eligibility criteria have been randomized to CET ($n = 29$) or EST ($n = 25$). An additional 19 individuals are on a waiting list for NIMH R01 funding to expand the trial to 100 additional adults with ASD. Individuals excluded from the study were primarily due to failure to meet inclusion criteria (39%), a lack of interest in participating in a research treatment trial (33%), and travel distance from the study (8%). It is our experience that when participants come to our program and are excluded for a lack of interest, it is the family members who are often most interested in their participation, but the participants themselves are not ready to consider enrolling in a randomized treatment trial.

Task 14 - Treatment Phase, participants treated with CET or EST (mos 6-42). All 52 of 54 individuals randomized to CET or EST have begun their study treatment condition with considerable success (2 randomized cases, 1 in CET and 1 in EST, terminated prior to treatment initiation). CET participants have begun receiving individual therapy, computer-based neurocognitive training, and group-based training in social cognition. The initial two cohorts of CET ($n = 14$) participants have completed all 45 social-cognitive group sessions, all of the neurocognitive training, and have completed 18-month (treatment completion) assessments. The initial two cohorts of EST participants ($n = 12$) have also completed individual stress management training and psychoeducation about ASD and have completed their 18-month (treatment completion) assessments during the same time frame. The third CET ($n = 8$) and EST ($n = 6$) cohorts have been receiving their treatment condition for 12-18 and are in the process of completing post-treatment assessments. The final CET ($n = 7$) and EST ($n = 7$) cohorts have begun the early phases of treatment and will complete 18 months by September, 2015.

Treatment satisfaction has been high, and while this is a long-term controlled trial, attrition has been low at 15%. To date, 8 individuals have been lost to attrition: 1 individual withdrew from CET at 9 months due to residential instability, 1 withdrew from CET at 9 months due to transportation issues, 1 withdrew from CET prior to 9 months due to increased employment, 1 withdrew from CET prior to beginning treatment due to a competing school obligations, 1 was administratively withdrawn from CET prior to 9 months due to significant behavioral and psychiatric instability; 1 withdrew from EST at study baseline due to lack of interest in the program, 1 was administratively withdrawn from EST due to low attendance, and 1 withdrew from EST prior to beginning treatment due to a family crisis. In addition, 2 early participants were withdrawn and allowed to switch treatment conditions prior to initiating treatment, because 1 CET participant had interest only in EST, and 1 EST participant had interest primarily in CET. These individuals were retained as "filler" participants in compassionate care in their desired condition, primarily to facilitate the formation of the first CET group. Given that the majority of attrition has occurred prior to beginning the interventions, treatment retention to date has been extraordinarily high at 91% (5 withdrew prior to beginning treatment, 3 withdrew after treatment exposure).

Task 15 - Follow-up testing (mos 12-48). Given the faster than expected rate of recruitment, we have been able to begin treatment with participants quickly and have been completing 9-month (mid-treatment) and 18-month (post-treatment) assessments with them as they progress through CET and EST. To date, 38 9-month assessments (21 in CET; 17 in EST) and 23 18-month assessments (11 in CET; 12 in EST) have been completed. These have included comprehensive batteries of neurocognition, social cognition, and adaptive function, as well as fMRI and structural neuroimaging assessments. For individuals who complete CET or EST, they will also be followed-up for 1-year post-treatment to assess treatment durability, which have already begun. To date, 14 participants have reached and completed their 30-month (1-year post-treatment) assessments (5 in CET; 9 in EST). *We anticipate needing a 1-year no-cost extension with minimal resources to complete 1-year (30 month) follow-up cognitive and behavioral collection on the remainder of the sample, and we have recently obtained funding from the Autism Research Institute to also support the collection of neuroimaging data as this sample reaches their 1-year post-treatment timepoint.*

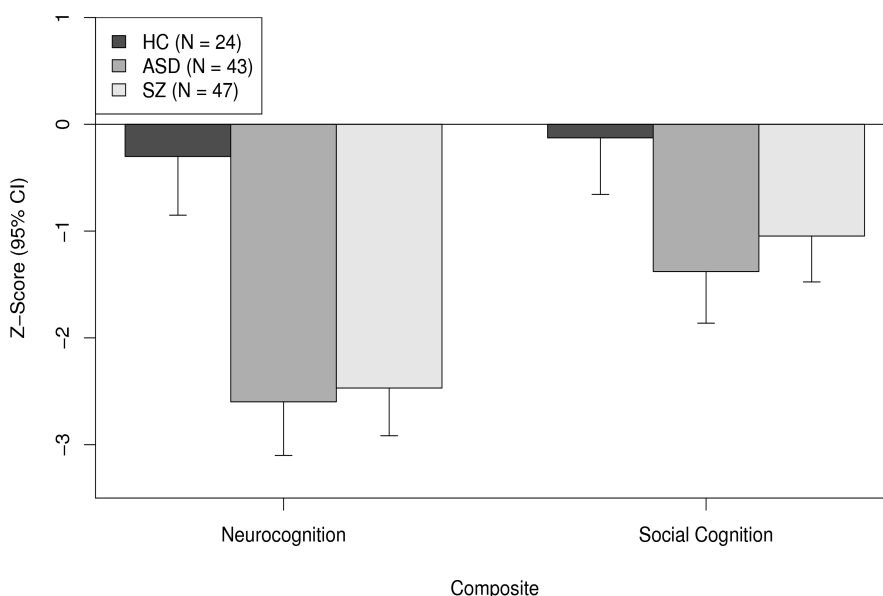
Task 16 - Volunteer Closeout and Final Feedback (mos 36-48). To be completed.

Task 17 - Preliminary and final data analyses of baseline data (mos 12-24). Pretreatment data among the 52 of the 54 (2 withdrew prior to treatment initiation and baseline data collection) individuals randomized to this trial have been completed and preliminarily analyzed. This consisted of comprehensive data collection on numerous measures of autism, cognition, and functional ability. No significant differences have emerged between CET and EST participants in demographic or pre-treatment cognitive characteristics. Perhaps most striking is the clear support these data provide for the need for an effective cognitive rehabilitation program for verbal adults with ASD by highlighting the broad impairments in cognition such individuals experience. As shown in **Table 1**, *overall* neurocognitive functioning for the sample was at the 29th percentile based on 50% normative performance. Although performance varied, significant impairments (at times as low as < 1%) were observed in all individuals across cognitive domains. Such findings indicate large impairments across multiple cognitive domains in this sample despite above-average IQ, which clearly supports the need for a comprehensive cognitive rehabilitation approach. Given the often overlooked cognitive deficits verbal adults with ASD experience, we have published a paper outlining these findings (Eack et al., 2013). In addition, we have demonstrated that the level of pre-treatment cognitive impairment experienced by adults with ASD (partially taken from this trial sample and the NIMH pilot sample) is highly deficient compared to healthy volunteers and is in fact, comparable to patients with schizophrenia across both social and non-social cognitive domains (see **Figure 1**; Eack et al., 2013). Taken together these findings increasingly indicate that verbal adults with ASD experience significant impairments in neurocognition and social cognition that are likely to be responsive to CET.

Table 1. Pre-Treatment Characteristics of Adults with ASD Randomized to an 18-Month Trial of CET or EST (N = 54).

Variable	CET (N = 29)		EST (N = 25)	
	M / N	SD / %	M / N	SD / %
Demographics				
Age	22.55	6.38	23.52	5.69
% Male	24	83%	23	92%
% College Educated	15	54%	17	81%
Full Scale IQ	107.97	14.35	106.24	15.30
Neurocognition Composite ^a	26.26	26.43	32.73	30.32
Processing Speed	40.12	33.45	45.70	34.40
Vigilance	33.97	28.71	42.48	36.17
Working Memory	33.85	23.66	31.49	31.27
Verbal Learning	29.65	28.49	44.26	30.80
Visual Learning	35.67	31.73	35.74	28.44
Reasoning	47.14	34.18	44.86	29.82
Social Cognition	29.12	23.17	36.25	28.82

^aComposites are given in percentile scores



Task 18 - Preliminary and final data analyses of 9 mos post-treatment data (mos 18-36). See Task 19.

Task 19 - Preliminary and final data analyses of outcome data at 18 mos (mos 24-48+). We have now published the preliminary pilot study of CET in 14 verbal adults with ASD and shown considerable levels of improvement in cognition and adaptive function (Eack et al., 2013). More rigorous results from interim analysis of this randomized controlled trial are also demonstrating significant promise as shown in **Figure 2**, which presents interim treatment findings on composite indices of neurocognitive, social-cognitive, and adaptive function using field standard measures administered by raters blind to treatment assignment. The neurocognitive composite consisted of the MATRICS Consensus Cognitive Battery. The social-cognitive composite consisted of the Mayer-Salovey-Caruso Emotional Intelligence Test, and the Penn Emotion Recognition Test, both performance-based measures of social cognition that have been well-validated in previous psychiatric research. The functional outcome composite consisted of standardized clinical interviews using the Social Adjustment Scale-II, Major Role Adjustment Inventory, and Social Responsiveness Scale. Composites were scaled with a mean (SD) of 50 (10) at baseline, with higher scores reflecting better performance. Analyses included all 40 participants who have reached their 9- or 18-month time point (22 in CET; 18 in EST), as well as those who have withdrawn early from treatment, to facilitate intent-to-treat

analysis. Results show medium-to-large levels of improvement in neurocognitive ($d = .79$) and social-cognitive ($d = .59$) function favoring CET at treatment completion compared to EST (see **Figure 2**). The greatest domains of neurocognitive improvement in CET were visual learning ($d = 1.17$) and processing speed ($d = .51$). The greatest area of social-cognitive improvement was in the domain of facial emotion perception ($d = .59$). *Most importantly, these cognitive gains observed in CET have translated into improvements on blind-rated measures of adaptive function*, with CET demonstrating large ($d = 1.27$) benefits that are approaching statistical significance in comparison to EST. Interestingly, EST participants are also demonstrating considerable gains ($d = .62$). Greatest areas of differential functional improvement favoring CET are major role functioning ($d = 1.02$) and employment ($d = .81$). As can be seen in **Figure 3**, while participants treated with EST are demonstrating difficulties in obtaining and maintaining competitive employment, those treated with CET are showing significantly greater gains in work, with over 50% competitively employed by the end of treatment. Taken together, these findings suggest that CET, a novel cognitive rehabilitation intervention, is having an impact on core cognitive deficits in ASD and that these gains are translating into meaningful improvements in functional outcome. Significant improvements, particularly in anxiety and depression are also being observed in EST, which is focusing on the stress-related aspects of ASD.

Consequently, it is expected that this trial will not only produce evidence supporting cognitive rehabilitation in adult ASD, but also the novel individual-based approach to stress regulation and illness management that is provided in EST.

Task 20 - Preliminary and final data analyses of outcome data 1-year post treatment (durability) (mos 36-48+). In addition to observing the active treatment effects of CET and EST on adults with ASD, we have also finished data collection and cleaning of 30-month (1-year post-treatment) durability data in 14 participants (5 in CET and 9 in EST). As can be seen in **Figure 4**, even in this preliminary sample, the social-cognitive and functional gains observed in CET at 18-months are being broadly maintained (and even slightly increasing) 1-year post-treatment. Significant differential benefits of CET on social cognition ($p = .046$) and functional outcome ($p = .003$) compared to EST are still clearly evident one year after completing treatment, indicating lasting benefits of cognitive remediation to this sample of adults with ASD. Maintenance of neurocognitive gains is currently less supported, with significant benefits in CET at 18 months, but some erosion of these one year after completing the study. It is possible that early neurocognitive improvement was necessary for social and functional change, but that lasting basic information processing improvements may not be required to maintain gains in adaptive function or may require ongoing periodic computerized intervention. As the follow-up sample grows, we will pay close attention to this issue, as it helps to elucidate the critical treatment targets for adults with ASD. Based in current low attrition, we estimate completing 26 additional 30-month assessments.

Figure 2. Effects of Cognitive Enhancement Therapy Versus Enriched Supportive Therapy on Composite Indexes of Neurocognition, Social Cognition, and Functional Outcome in Adults with ASD (N = 40)

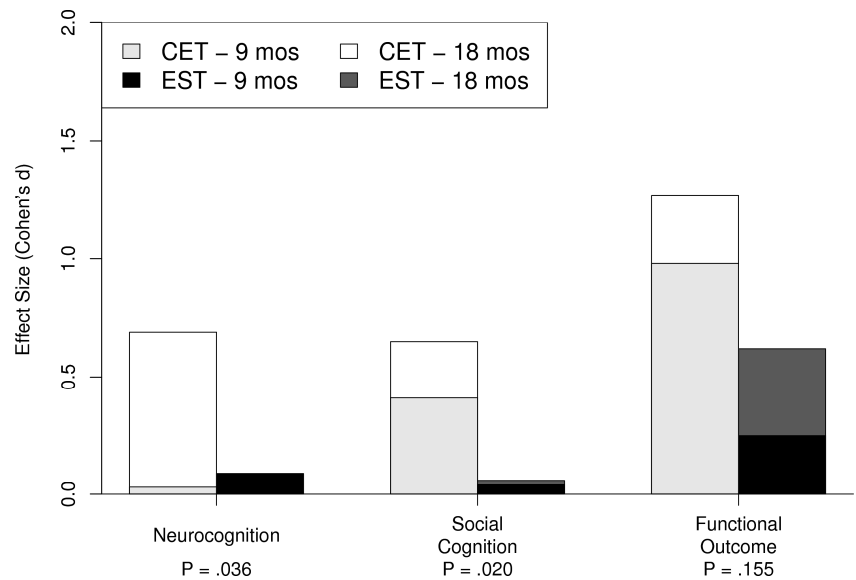
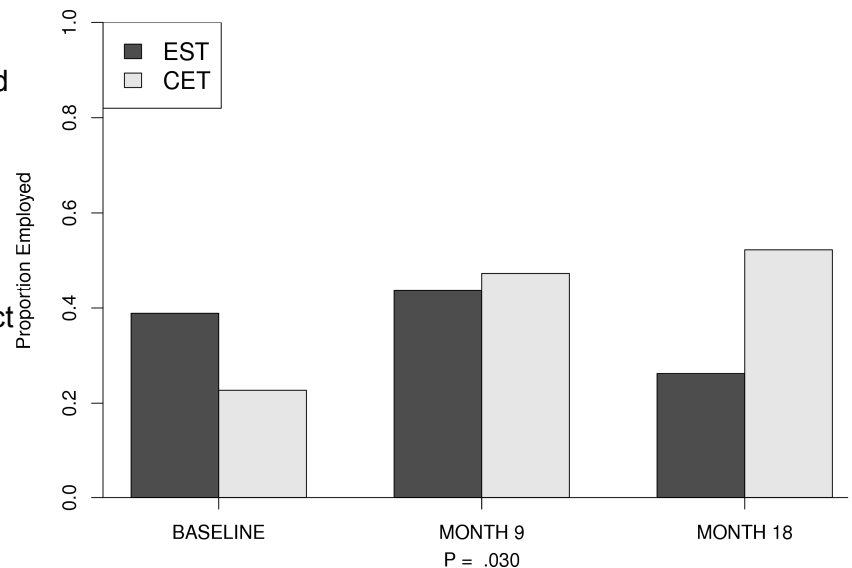


Figure 3. Effects of Cognitive Enhancement Therapy Versus Enriched Supportive Therapy on Competitive Employment in Adults with ASD (N = 40)



It is also important to note that while improvements in functional outcome in EST are modest compared to CET, EST-related improvements in this domain are also being maintained at 1-year post-treatment. These preliminary findings suggest the long-term benefits of cognitive remediation and stress management/affect regulation interventions on critical outcomes in adults with autism, and indicate a striking maintenance of treatment gains not commonly observed with psychosocial interventions. *Given the length of this follow-up, we anticipate needing to enter a 1-year no-cost extension to complete remaining 30-month assessments.*

Task 21 - Analyses of fMRI data at baseline (mos 6-24).

Pre-treatment MRI data have been collected with processing speed, perspective-taking, theory of mind, and emotion regulation fMRI measures on participants randomized since Autism Speaks support for the imaging studies began. Of the 54 individuals randomized in this DoD trial, 12 were recruited and randomized before the imaging studies began with funding from Autism Speaks. While these 12 individuals did not receive baseline MRI scans, treatment completion MRI data will continue to be collected on them, which will be compared with a healthy control sample to facilitate post-treatment analyses of CET effects on neural function and connectivity. Of the remaining individuals, 39 have completed their baseline MRI and 1 could not complete the MRI due to claustrophobia that was not apparent at screening using the mock scanner. In addition, 20 healthy volunteers have completed identical scanning procedures. Results of comparisons between adults with ASD and healthy volunteers at baseline have helped provide standardization estimates for healthy brain function and regions of interest for areas that are most likely to be affected by CET.

As can be seen in **Figure 5**, expected regions of interest in social-cognitive brain networks are showing consistent abnormalities in the sample of adults with ASD compared to healthy controls across the 4 tasks. For the emotion regulation task, participants with ASD are showing widespread reduced activity in the bilateral insula, as well as the cingulate gyrus during the frustration components of this task compared to controls, indicating difficulty in regulating fronto-temporal circuitry in support of emotion regulation (**Figure 5a**). For the theory of mind task, ASD participants are demonstrating significant hypofunction in the medial prefrontal cortex during mentalizing conditions compared to controls, potentially signifying greater difficulty in recruiting this circuitry during theory of mind (**Figure 5b**). Similar temporal hypofunction was found in the bilateral superior temporal gyrus for the perspective-taking task, where those with autism demonstrated significantly reduced activation in this region during perspective-taking than controls (**Figure 5c**). Such findings consistently suggest difficulty among adults with ASD in recruiting theory of mind and perspective-taking circuitry to understand the mental states of others. For the processing speed task, individuals with ASD are demonstrating significantly *increased* medial and lateral prefrontal activity in simple versus choice reaction time trials, indicating a potential inefficient prefrontal response to increased processing speed demands (**Figure 5d**). All of these findings not only provide loci for subsequent treatment effect analyses, but also elucidate social-cognitive brain dysfunction that may be indicative of the pathophysiology of ASD and will be the focus of subsequent published reports.

Figure 4. One-Year Durability of Cognitive Enhancement Therapy and Enriched Supportive Therapy Effects on Composite Indexes of Neurocognition, Social Cognition, and Functional Outcome in Adults with ASD (N = 14)

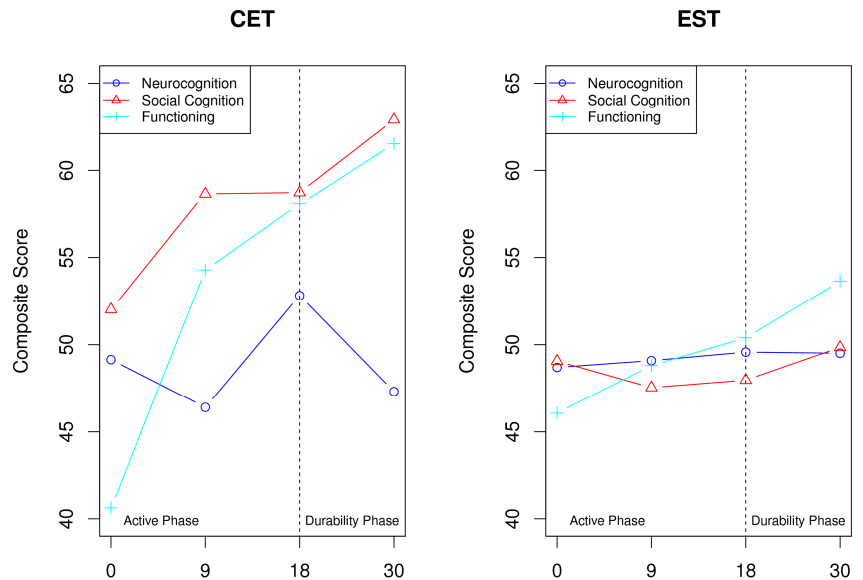


Figure 5. Functional Brain Activity Differences Between Adults with Autism Spectrum Disorder ($N = 39$) and Healthy Volunteers ($N = 20$).

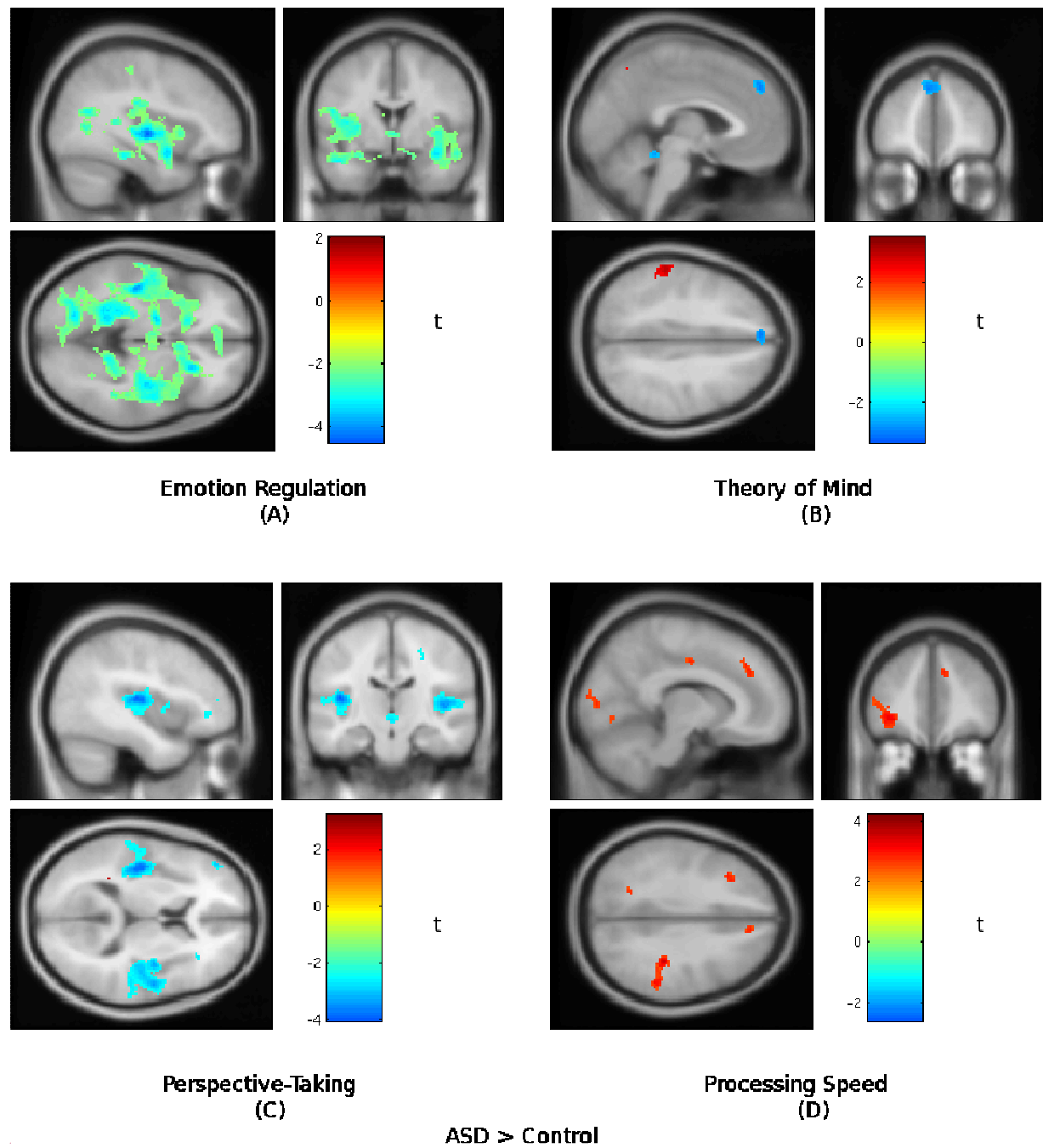
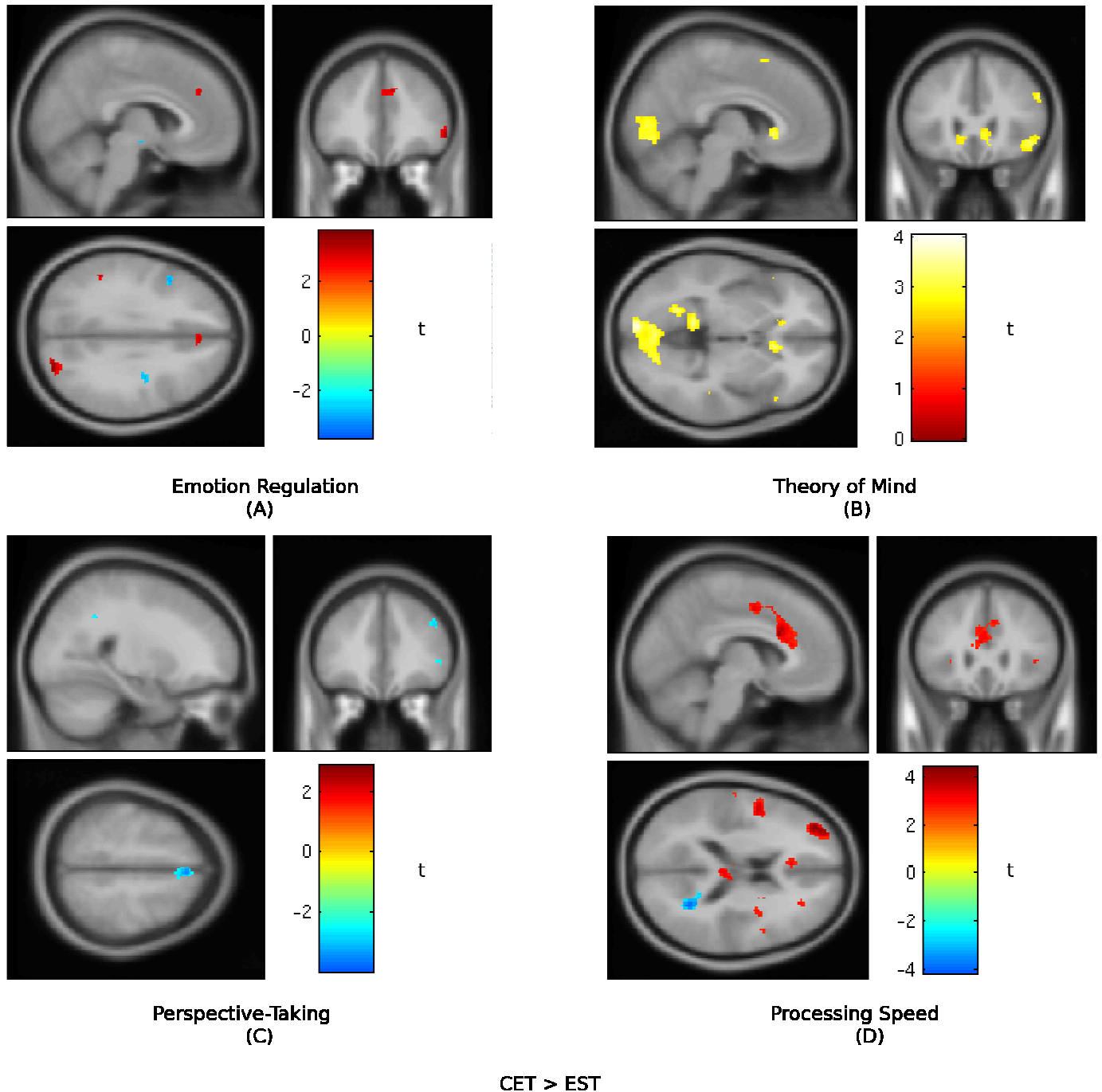


Figure 6. Preliminary Effects of CET versus EST on Brain Function ($N = 30$).



Task 22 - Analyses of fMRI data at 18 mos (mos 25-48). Preliminary post-treatment (9- or 18-month, depending on length of enrollment) analyses of all fMRI tasks have been completed in 30 participants (17 in CET; 13 in EST). As can be seen in **Figure 6a**, those treated with CET are demonstrating significant differential increases in brain activity in the cingulate and right orbitofrontal cortex during our emotion regulation task, suggesting an increase in emotion regulation circuitry function during the course of CET compared to those treated with EST. **Figure 6b** presents treatment x time interactions favoring CET improvement over EST during our theory of mind task, where participants treated with CET are showing widespread and robust increases in medial prefrontal (anterior cingulate), orbitofrontal, and ventromedial prefrontal cortical activity, all of which are key regions in the theory of mind network. Interestingly, the medial prefrontal hypoactivity that was observed compared to controls at baseline appears to not have significantly changed, but rather participants treated with CET are showing improvement in surrounding medial prefrontal areas. This is the first evidence to suggest that social-cognitive enhancement in ASD may be partially reliant upon strengthening supporting compensatory networks. **Figure 6c** presents areas of differential *decrease* in activation during our

perspective-taking task. Prominent increases in BOLD-signal activity were not observed in CET compared to EST during this task. However, medial and lateral prefrontal decreases were observed in CET compared to EST participants. The medial prefrontal decreases center primarily around the supplementary motor area, which could suggest easier coordination of basic movement processes in completing the task or in simulating the perspective of the other person during the task. Decreased activation on the dorsolateral and ventrolateral prefrontal cortex suggest decreased executive/problem-solving effort needed to complete the perspective-taking task, perhaps due to improved coordination with theory of mind circuitry. These issues will be more thoroughly examined in functional connectivity analyses as the study sample reaches treatment completion. Finally, **Figure 6d** presents data on treatment x time interactions for our processing speed task, in which CET participants are demonstrating large and significant increases in numerous fronto-temporal brain networks supporting attention and executive function, including the insula, cingulate, and lateral prefrontal cortices. Results suggest an important increase in executive and attentional control functions during the task that is improving speed of processing in CET participants. Correlations with cognitive and behavioral data will be forthcoming and are expected to connect these changes in brain function to improved social and non-social cognitive processes. While preliminary, these findings support the feasibility of elucidating and characterizing the neural mechanisms of response to cognitive rehabilitation in adults with ASD, and indicate the potential of neuroplasticity well into adulthood in these disorders.

Task 23 - Prepare final report of results for funder (mos 42-48). To be completed.

Task 24 - Prepare newsletter of results for all participants (mos 12, 24, 36, 48). The first two cohorts of participants in the study have now completed 18-month assessments and we are preparing a newsletter of these findings to distribute to participants and their family members.

Task 25 - Prepare report for distribution by Autism Speaks (mos 12, 24, 36, 48). A final report has been prepared and submitted to Autism Speaks outlining recruitment accomplishments and primary study outcomes.

Task 26 - Prepare large scale study for NIH multi-site RO1 guided by results of above study with new hypotheses guiding new advances in treatment. An R01 application proposing a large-scale efficacy trial has been developed, submitted, and reviewed by NIMH as of October 14, 2014. While we are awaiting for specific feedback from reviewer comments and program officers at NIMH, the application received a positive score of 28 on this first submission.

Task 27 - Dissemination of findings to lay and scientific audiences throughout the third and fourth years as evidence for each cohort is completed. We have begun disseminating findings to scientific audiences including presenting at the 2014 IMFAR, and we plan to present the latest results from this trial at the upcoming 2015 IMFAR and other scientific meetings. We have also begun to disseminate preliminary findings to clinical and parent/patient audiences, including with representatives from the Autism Bureau of the Commonwealth of Pennsylvania and to agencies throughout the Western Pennsylvania region.

Task 28 - Recruitment of healthy volunteers (N = 40) (mos 12-36). We have created a sub-study brochure and advertisements for healthy volunteers, received IRB approval for these materials, and with the support of the ACE, contacted healthy volunteers in our previous studies as well as wider research registries and the community. This has given us access to a large pool of potentially eligible healthy volunteers from which to draw our sample. We have completed recruitment of 20 healthy volunteers and have found that sample size to be sufficient for defining normative neural responses on our fMRI tasks.

Task 29. Screen healthy volunteers for eligibility (mos 12-36). We have currently screened 29 healthy volunteers and matched them to the current sample of trial participants. Of these individuals screened, 20 have completed all aspects of their participation in the study.

Task 30. Collect cross-sectional neuroimaging data in healthy volunteers (mos 12-36). We have currently completed neuroimaging data collection on all 20 age- and gender-matched healthy volunteers.

Task 31. Collect cross-sectional cognitive and clinical data in healthy volunteers (mos 12-36). We have currently completed cognitive and clinical data collection on all 20 age- and gender-matched healthy volunteers.

3. KEY RESEARCH ACCOMPLISHMENTS

- Identification of core deficits in elementary cognitive abilities in verbal adults with autism, despite intact levels of intelligence
- Identification of cross-diagnostic similarities in cognitive deficits in ASD and schizophrenia, the disorder for which the efficacy of CET and EST were previously demonstrated and the disorder with which verbal adults with ASD are often misdiagnosed
- Adaptation of two promising intervention approaches (CET and EST) to adults with ASD
- Completion of recruitment and randomization of all 54 adults with ASD proposed for this controlled clinical trial
- Significant and medium-to-large differential levels of social and non-social cognitive improvement favoring participants treated with CET, but with significant improvements in EST as well
- Promising results demonstrating large levels of improvement in social adjustment among *both* CET and EST treated participants, with significant advantages in major role adjustment and employment in CET compared to EST
- Identification of significant differential changes in underlying neural circuitry in CET compared to EST participants reflecting neuroplastic changes in social-cognitive brain networks modulated by cognitive rehabilitation

4. REPORTABLE OUTCOMES

- Manuscripts, abstracts, presentations:
 1. Eack, S. M., Mazefsky, C. A., Minshew, N. J. (in press). Misinterpretation of facial expressions of emotion in verbal adults with autism spectrum disorder. *Autism*.
 2. Bishop-Fitzpatrick, L., Mazefsky, C. A., Minshew, N. J., & Eack, S. M. (in press). The relationship between stress and social functioning in adults with autism spectrum disorder and without intellectual disability. *Autism Research*.
 3. Eack, S. M., Greenwald, D. P., Hogarty, S. S., Bahorik, A. L., Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J. (2013). Cognitive Enhancement Therapy for adults with autism spectrum disorder: Results of an 18-month feasibility study. *Journal of Autism and Developmental Disorders*, 43(12), 2866-2877.
 4. Eack, S. M., Bahorik, A. L., Hogarty, S. S., Greenwald, D. P., Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J. (2013). Is cognitive rehabilitation needed in verbal adults with autism? Insights from initial enrollment in a trial of Cognitive Enhancement Therapy. *Journal of Autism and Developmental Disorders*, 43(9), 2233-2237.
 5. Eack, S. M., Bahorik, A. L., McKnight, S. A. F., Hogarty, S. S., Greenwald, D. P., Newhill, C. E., Phillips, M. L., Keshavan, M. S., & Minshew, N. J. (2013). Commonalities in social and non-social cognitive impairments in adults with autism spectrum disorder and schizophrenia. *Schizophrenia Research*, 148(1-3), 24-28.
 6. Fitzpatrick, L. B., Minshew, N. J., & Eack, S. M. (2013). A systematic review of psychosocial interventions for adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 43(3), 687-694.
 7. Eack, S. M., Greenwald, D. P., Hogarty, S. S., Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J. (2014, May). Cognitive Enhancement Therapy for adults with autism spectrum disorder: Results of an 18-month feasibility study. Paper presented at the annual International Meeting for Autism Research, Atlanta, GA.
 8. Bishop-Fitzpatrick, L., Minshew, N. J., & Eack, S. M. (2014, May). The relationship between social cognition and social functioning in individuals with autism spectrum disorder. Poster presented at the annual International Meeting for Autism Research, Atlanta, GA.
 9. Bishop-Fitzpatrick, L., Minshew, N. J., & Eack, S. M. (2014, May). The relationship between stress and social functioning in individuals with autism spectrum disorder. Poster presented at the annual

- Licenses applied for and/or issued: None
- Degrees obtained that are supported by this award: None
- Development of cell lines, tissue or serum repositories: None
- Informatics such as databases and animal models, etc:
 1. NDAR-compatible database
 2. Subject tracking database
- Funding applied for based on work supported by this award:
 1. R01 MH-106450, Eack (PI), Cognitive Enhancement Therapy for Adult Autism Spectrum Disorder, NIH/NIMH (First submission priority score - 28)
 2. Autism Research Institute, Eack and Minshew (PIs), Durability of Neuroplasticity Changes From Cognitive Enhancement Therapy in Adults with Autism Spectrum Disorder (Awarded)
- Employment or research opportunities applied for and/or received based on experience/training supported by this award:
 1. K23 MH-95783, Eack (PI), Social-Cognitive Rehabilitation and Brain Function in Early Schizophrenia, NIH/NIMH (Awarded)
 2. R01 MH-92440, Keshavan & Eack (PIs), Brain Imaging, Cognitive Enhancement and Early Schizophrenia, NIH/NIMH (Awarded)

5. CONCLUSION

This research is dedicated to the conduct of the first randomized-controlled trial of a comprehensive cognitive rehabilitation intervention in verbal adults with ASD. Cognitive rehabilitation has been shown to be effective in many other neurological conditions, and Cognitive Enhancement Therapy (CET) in particular has demonstrated considerable success in patients with schizophrenia who share similar social-cognitive and neurocognitive impairments. Because there was no community treatment as usual for verbal adults with ASD, we designed an enriched supportive treatment approach for this trial, which focused on understanding the disorder and managing stress and emotions. As a result, this study assesses the comparative efficacy of two new treatment approaches for verbal adults with ASD. Study findings to date indicate that (1) the population of verbal adults with ASD is in great need of cognitive rehabilitation, exhibiting medium to large deficits in a variety of social and nonsocial cognitive domains; (2) CET and EST can be feasibly implemented with adults with ASD with minimal attrition and high degrees of satisfaction; (3) CET offers a potentially highly significant advantage over routine supportive therapies in its ability to improve cognitive and functional outcomes in this population; and (4) CET may achieve its benefits on social and non-social cognition through altering neural networks that underlie these abilities.

So What? The need for interventions to treat the core cognitive problems present in adults with ASD is great. Individuals with ASD live 60 years of their lives as adults and yet there are no existing evidence-based treatments. The potential, especially for high functioning adults with ASD, to have productive and satisfying lives certainly exists but will not be achieved without more effective interventions. CET is a cognitive rehabilitation intervention that aims to address the core cognitive impairments that markedly limit adaptive behavior, work capacity, and independent functioning in adults with ASD. The intervention is provided over a long-term, 18-month period, which is necessary to address the entrenched behavior patterns that many adults with ASD experience. This project is significant in that it is, for the first time, systematically testing the efficacy of a comprehensive cognitive rehabilitation approach in ASD in comparison to an Enriched Supportive Therapy (EST). Current findings suggest that there are benefits of both CET and EST to adults with ASD, pointing to novel avenues for effective intervention on core deficits in this population. While a considerable advantage of CET over EST is being demonstrated on numerous domains, non-trivial levels of improvement in adjustment and adaptive function are also being observed in those treated with EST. Ultimately it is expected that this investigation will result in significant treatment advances for this highly underserved group of individuals.

6. REFERENCES

1. Eack, S. M., Greenwald, D. P., Hogarty, S. S., Bahorik, A. L., Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J: Cognitive Enhancement Therapy for adults with autism spectrum disorder: Results of an 18-month feasibility study. *Journal of Autism and Developmental Disorders*, 43:2866-2877, 2013
2. Eack, S. M., Wojtalik, J. A., Newhill, C. E., Keshavan, M. S., Phillips, M. L: Prefrontal cortical dysfunction during visual perspective-taking in schizophrenia. *Schizophrenia Research*, 150:491-497, 2013
3. Eack, S. M., Bahorik, A. L., Hogarty, S. S., Greenwald, D. P., Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J: Is cognitive rehabilitation needed in verbal adults with autism? Insights from initial enrollment in a trial of Cognitive Enhancement Therapy. *Journal of Autism and Developmental Disorders* 43:2233-2237, 2013
4. Eack, S. M., Bahorik, A. L., McKnight, S. A. F., Hogarty, S. S., Greenwald, D. P., Newhill, C. E., Phillips, M. L., Keshavan, M. S., & Minshew, N. J: Commonalities in social and non-social cognitive impairments in adults with autism spectrum disorder and schizophrenia. *Schizophrenia Research* 148:24-28, 2013
5. Eack, S. M., Greenwald, D. P., Hogarty, S. S., Cooley, S. J., DiBarry, A. L., Montrose, D. M., & Keshavan, M. S: Cognitive Enhancement Therapy for early-course schizophrenia: Effects of a two-year randomized controlled trial. *Psychiatric Services* 60:1468-1476, 2009
6. Eack, S. M., Hogarty, G. E., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S: Effects of Cognitive Enhancement Therapy on employment outcomes in early schizophrenia: Results from a two-year randomized trial. *Research on Social Work Practice* 21:32-42, 2011
7. Epley, N., Morewedge, C. K., & Keysar, B: Perspective taking in children and adults: Equivalent egocentrism but differential correction. *Journal of Experimental Social Psychology* 40:760-768, 2004
8. Fitzpatrick, L. B., Minshew, N. J., & Eack, S. M: A systematic review of psychosocial interventions for adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders* 43:687-694, 2013
9. Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Keshavan, M., Cooley, S., DiBarry, A. L., Garrett, A., Parepally, H., & Zoretich, R: Cognitive enhancement therapy for schizophrenia. Effects of a 2-year randomized trial on cognition and behavior. *Archives of General Psychiatry* 61:866-876, 2004
10. Mason, R. A., Williams, D. L., Kana, R. K., Minshew, N., & Just, M. A: Theory of Mind disruption and recruitment of the right hemisphere during narrative comprehension in autism. *Neuropsychologia* 46:269-280, 2008
11. Perlman, S. B., & Pelphrey, K. A: Developing connections for affective regulation: Age-related changes in emotional brain connectivity. *Journal of Experimental Child Psychology* 108:607-620, 201